

Predictors of poor outcomes in 488 patients with herb-induced liver injury

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ABSTRACT

Background/Aims: Herb-induced liver injury (HILI) can lead to chronic liver injury, liver transplantation, or even death. This study aimed to identify the predictors of poor HILI outcomes, especially chronic HILI.

Materials and Methods: Clinical data of 488 patients with HILI were retrospectively analyzed from a Chinese center between January 2010 and January 2014. Logistic regression and C-statistic were used to identify risk factors and prognostic models for HILI outcomes.

Results: In all patients, 69 (14.1%) developed chronic HILI, and 20 (4.1%) died due to liver injury or underwent liver transplantation. To predict the fatal HILI prognosis, the model for end-stage liver disease (MELD) with a C-statistic of 0.981 (95%CI 0.968-0.995) was better than Hy's law (C-statistic 0.569; 95%CI 0.449-0.689). The latency, course of peak alanine aminotransferase decreasing $\geq 50\%$ after discontinuation of herb application, peak triglyceride value, and platelet count at liver injury onset were identified as independent risk factors for chronicity with the adjusted odds ratios of 1.268 (95% confidence interval [CI] 1.034-1.554), 2.303 (95%CI 1.588-3.340), 0.580 (95%CI 0.343-0.978), and 0.183 (95%CI 0.091-0.368), respectively. A prognostic model for chronic HILI based on these four factors yielded the best prediction with a C-statistic of 0.812 (95%CI 0.755-0.868), compared with MELD (C-statistic 0.506; 95%CI 0.431-0.581) and Hy's law (C-statistic 0.418; 95%CI 0.343-0.492).

Conclusion: Model for end-stage liver disease can be used to predict the fatal prognosis of HILI. A long latency, slow recovery, and low triglyceride value and platelet counts are important determinants for chronic HILI.

Keywords: Drug-induced liver injury, herbal hepatotoxicity, mortality, chronicity, prognosis

INTRODUCTION

Herb-induced liver injury (HILI) has increasingly been reported and attracted the attention of physicians, pharmaceutical companies, and regulatory agencies over the past years (1,2). In general, HILI is self-limited after withdrawing implicated herbs or herbal products; however, in some cases, chronic liver injury, liver transplantation, or even death is observed (3,4). In a previous case collection about the outcomes of HILI, 70 (12.4%) of 563 patients developed chronic HILI; 29 (5.2%) underwent liver transplantation or died from liver injury (3). Until now, only a few studies tried to survey clinical characteristics of HILI patients with poor outcomes and define risk factors for poor HILI prognosis (5). Thus, it is still challenging to predict the HILI prognosis and guide its treatment (2,5).

In this study, we retrospectively analyzed the clinical data of 488 patients diagnosed with HILI to identify the risk factors and prognostic models for severe HILI cases, especially development of chronic HILI.

MATERIALS AND METHODS

All patients admitted to our hospital (Beijing, China) due to liver injury between January 2010 and January 2014 were included. HILI was diagnosed based on the following criteria (2,5,6); (i) recent onset of a rise in alanine aminotransferase (ALT) $\geq 5 \times$ upper limit of normal (ULN) or alkaline phosphatase (ALP) $\geq 2 \times$ ULN, or a rise in total serum bilirubin (TB) ≥ 2 mg/dL associated with ALT $\geq 3 \times$ ULN; (ii) exclusion of viral hepatitis, autoimmune liver disease, alcoholic liver disease, metabolic disorders, bile duct obstruction, and other nontoxic causes of liver diseases by laboratory tests (anti-hepatitis A virus IgM, hepatitis B surface antigen, anti-hepatitis B core IgM, anti-hepatitis C virus, hepatitis C virus RNA, and anti-hepatitis E virus IgM, anti-hepatitis E virus IgG, anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, ceruloplasmin, and α -1-antitrypsin), radiological examinations, and/or liver biopsy; (iii) exclusion of pre-existing liver diseases; (iv) a medical history with only exposure to

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herbs or herbal products within the previous 6 months before the onset of an abnormal liver test; (v) a Roussel Uclaf Causality Assessment Method (RUCAM) score ≥ 3 points. All data of patients diagnosed with HILI were extracted from our hospital records, including a detailed history of liver injury events and exposure to the implicated herb(s). Missing or unclear information was clarified with physicians.

All HILI cases were divided into three groups: (i) healed HILI, including patients who had persistent normal liver function after implicated herb(s) discontinuation; (ii) chronic HILI, including patients with sustained liver-related laboratory, radiologic, or histologic abnormalities at 6 months after the HILI onset (5); (iii) fatal HILI, including patients who underwent liver transplantation or died from HILI. HILI was classified as hepatocellular, cholestatic, or mixed pattern, based on the determination of the ratio R of ALT (as a multiple of the ULN) to ALP (as a multiple of the ULN) (7). The model for end-stage liver disease (MELD) score was calculated as follows: $9.6 \times \ln[\text{creatinine (mg/dL)}] + 3.8 \times \ln[\text{bilirubin (mg/dL)}] + 11.2 \times \ln(\text{international normalized ratio}) + 6.4$ (8). The positivity for Hy's law was defined

as either ALT or AST $\geq 3 \times \text{ULN}$, and TB $\geq 2 \times \text{ULN}$ (2). The definition of re-challenge is for the hepatocellular pattern ALT level before re-exposure was $< 5 \times \text{ULN}$ and after re-exposure increased $\geq 2 \times \text{ALT}$ level before re-exposure, while for cholestatic or mixed pattern ALP level before re-exposure was $< 2 \times \text{ULN}$ and after re-exposure increased $\geq 2 \times \text{ALP}$ level before re-exposure (6).

Statistics analysis

Continuous variables were described with mean \pm standard deviation (SD) and median values including the 25th and 75th percentile values, and they were analyzed with the one-way analysis of variance for normally distributed values or the Kruskal-Wallis test for skewed distributions to calculate significant differences. Frequency and percentages were used to describe categorical variables, and a chi-squared test was used for comparison. To predict the fatal prognosis of HILI, MELD and Hy's law were compared, and receiver operating characteristics (ROC) curve in the form of C-statistic with 95% confidence interval (CI) was used to describe their predictive abilities. To identify the predictors of chronicity, a multivariate logistic regression analysis including variables based on a univariate analysis with $p < 0.10$ and clinical judgment was conducted. The results were reported as adjusted odds ratio (OR) with 95% CI. Based on the multivariate logistic regression analysis, a model for chronic HILI was developed and compared with MELD and Hy's law. The C-statistic with 95% CI was used to assess the discriminative accuracy of these models for chronic HILI. A $p < 0.05$ was recognized as statistically significant. All statistical analyses were performed using the SPSS (Statistical Package for the Social Sciences) version 16.0 software (SPSS Inc.; Chicago, IL, USA).

RESULTS

Demographic features

From January 2010 to January 2014, a total of 61,516 patients were hospitalized due to liver injury, but 49,724 cases fulfilled the clinical biochemistry criteria for HILI; a total of 40,683 patients were diagnosed with viral hepatitis, alcoholic hepatitis, autoimmune liver diseases, metabolic disorders, or other liver diseases; 7,787 cases were combined with pre-existing liver diseases; the liver injury in 759 patients was caused by synthetic drug(s) or a combination of synthetic drug(s) and herb(s); all of them were not eligible for this study. In 495 patients only exposed to herb(s) before the onset of abnormalities in liver function, 52 (10.5%) cases were considered high probable according to RUCAM, 370 (74.8%) were probable, 66 (13.3%) were

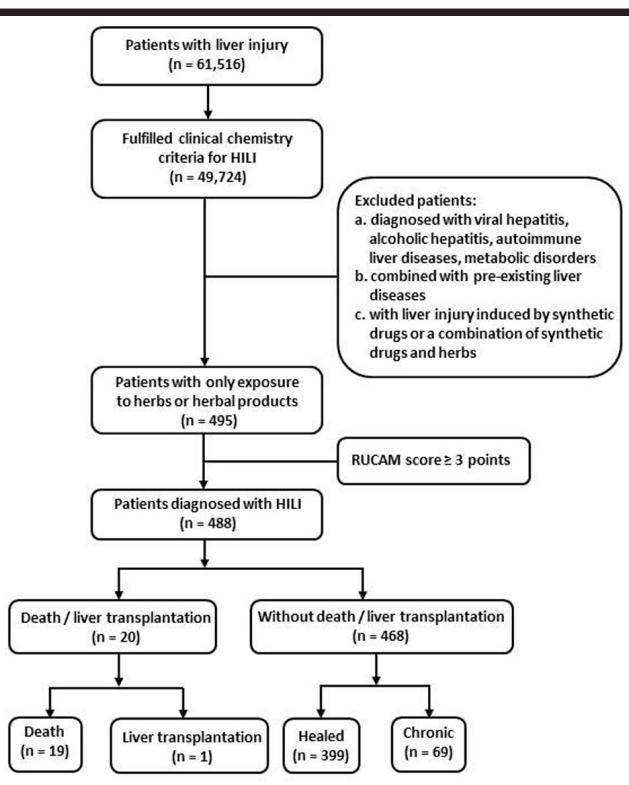


Figure 1. The diagnosis and prognosis of patients with HILI
HILI: Herb-induced liver injury

Table 1. Characteristics of the 488 patients with HILI: comparisons according to the liver injury patterns

Characteristics	Total (n=488)	Hepatocellular (n=420)	Cholestatic (n=31)	Mixed (n=37)	p
Age (y), mean±SD	45±13	43±13	54±16	51±13	<.001
Proportion of patients aged 65 years or older, %	6.4	4.3	19.4	18.9	<.001
Female, %	71.5	71.0	61.3	86.5	0.057
Alcohol use*, %	12.1	13.1	12.9	0.0	0.030
Allergy history, %	15.8	15.2	22.6	16.2	0.486
Latency (d), median (25 th , 75 th)	30 (15, 63)	30 (15, 60)	60 (30, 1100)	30 (10, 75)	0.010
Course of peak ALT decreasing ≥50% after herbal intake discontinuation, median (25 th , 75 th)	7 (5, 11)	7 (5, 8)	18 (10, 30)	12 (6, 21)	<.001
Positive re-challenge, %	7.2	7.6	0.0	8.1	0.313
Fever, %	6.8	6.9	3.2	8.1	0.788
Skin rashes, %	2.9	2.9	0.0	5.4	0.455
Biochemistries, mean±SD					
Peak ALT (U/L)	935±672	1050±649	118±122	311±263	<.001
Peak ALP (U/L)	186±115	168±72	341±263	264±178	<.001
Peak TB (mg/dL)	10.7±9.2	10.6±9.0	12.2±11.1	10.7±9.9	0.740
Lowest ALB (g/L)	37±5	37±5	31±5	35±6	<.001
Peak Scr (μmol/L)	77.6±34.8	75.7±21.6	97.7±99.8	82.0±47.5	0.362
Peak TG (mmol/L)	2.08±1.25	2.08±1.21	1.90±1.46	2.20±1.54	0.724
Peak TC (mmol/L)	3.89±1.78	3.72±1.30	4.92±4.02	4.94±2.71	0.012
Peak INR	1.19±0.48	1.18±0.49	1.25±0.40	1.21±0.45	0.729
Blood routine at onset, mean±SD					
White blood cell count (×10 ⁹ /L)	5.76±2.28	5.73±2.27	5.19±1.86	6.46±2.69	0.115
Eosinophil count (×10 ⁹ /L)	0.24±0.29	0.23±0.27	0.24±0.17	0.26±0.50	0.819
Platelet count (×10 ⁹ /L)	209±84	210±80	179±104	218±104	0.242
MELD score, mean±SD	13.2±7.2	13.1±7.0	14.7±8.0	13.0±8.7	0.485
Hy's law, %	66.8	74.0	6.5	35.1	<.001
Cirrhosis, %	7.6	5.0	35.5	13.5	<.001
Prognosis, %					
Healed	81.8	85.7	45.2	67.6	
Chronic	14.1	10.7	45.2	27.0	
Fatal	4.1	3.6	9.7	5.4	

*The patients had a drinking history (alcohol intake of >2 drinks per day for women and >3 drinks per day for men) but did not drink a month before the liver injury

ALT: alanine transaminase; ALP: alkaline phosphatase; TB: total bilirubin; ALB: albumin; Scr: serum creatinine; TG: triglyceride; TC: total cholesterol; INR: international normalized ratio; MELD: model for end-stage liver disease

possible, 7 (1.4%) were unlikely, and no cases were excluded. The diagnostic criteria of HILI are presented in Figure 1.

Clinical characteristics

Out of 488 patients who fulfilled the diagnostic criteria of HILI, 420 (86.1%) cases were classified as hepa-

tocellular, 31 (6.3%) as cholestatic, and 37 (7.6%) as a mixed pattern of liver injury; clinical characteristics are summarized in Table 1. The mean age was 45 years (range, 15–89), with 480 (98.4%) adults (≥18 years). With respect to the time from the beginning of herb application to the onset of liver injury, 27 (5.5%) cases

Table 2. Characteristics among the HILI cases with short and long latency

Characteristics	Short Latency (<5 days) (n=27)	Long Latency (>90 days) (n=90)	p
Age (y), mean±SD	43±16	44±15	0.650
Proportion of patients aged 65 years or older, %	7.4	8.9	1.000
Female, %	74.1	74.4	0.969
Alcohol use*, %	11.1	7.8	0.695
Allergy history, %	18.5	20.0	0.865
Course of peak ALT decreasing ≥50% after herbal intake discontinuation, median (25 th , 75 th)	7 (6, 11)	7 (5, 15)	0.735
Positive re-challenge, %	22.2	2.2	0.002
Fever, %	14.8	3.3	0.049
Skin rashes, %	7.4	0.0	0.052
Biochemistries, mean±SD			
Peak ALT (U/L)	859±672	682±554	0.170
Peak ALP (U/L)	226±195	165±105	0.037
Peak TB (mg/dL)	14.0±10.6	9.2±9.4	0.027
Lowest ALB (g/L)	36±4	36±7	0.616
Peak Scr (μmol/L)	76±31	82±61	0.605
Peak TG (mmol/L)	2.19±1.45	1.72±1.33	0.115
Peak TC (mmol/L)	4.21±2.34	3.69±1.44	0.161
Peak INR	1.41±1.10	1.25±0.60	0.478
Blood routine at onset, mean±SD			
White blood cell count (×10 ⁹ /L)	6.64±3.70	5.30±2.25	0.084
Eosinophil count (×10 ⁹ /L)	0.24±0.26	0.17±0.12	0.225
Platelet count (×10 ⁹ /L)	213±73	185±88	0.136
Clinical pattern, %			0.583
Hepatocellular	85.2	75.6	
Cholestatic	7.4	15.6	
Mixed	7.4	8.9	
MELD score, mean±SD	15.2±8.6	12.8±8.1	0.190
Hy's law, %	70.4	53.3	0.117
Cirrhosis, %	3.7	21.1	0.041
Prognosis, %			0.032
Healed	74.1	64.4	
Chronic	14.8	33.3	
Fatal	11.1	2.2	

* The patients had a drinking history (alcohol intake of >2 drinks per day for women and >3 drinks per day for men) but did not drink a month before the liver injury

ALT: alanine transaminase; ALP: alkaline phosphatase; TB: total bilirubin; ALB: albumin; Scr: serum creatinine; TG: triglyceride; TC: total cholesterol; INR: international normalized ratio; MELD: model for end-stage liver disease

had a short latency (<5 days), and 90 (18.4%) had a long latency (>90 days); all clinical characteristics are listed in Table 2. After withdrawal of the suspected herbs, 399 (81.8%) patients achieved sustained nor-

malization of liver biochemistry, 69 (14.1%) developed chronic HILI, 37 (7.6%) cirrhosis, 1 (0.2%) patient underwent liver transplantation, and 19 (3.9%) died due to their liver injury.

Table 3. Comparison of characteristics between the death/liver transplantation group and the healed/chronic group

Characteristic	Death/Liver Transplantation (n=20)	Healed/Chronic (n=468)	p
Age (y), mean±SD	47±16	45±13	0.468
Proportion of patients aged 65 years or older, %	15.0	6.0	0.127
Females, %	70.0	71.6	0.878
Alcohol use*, %	5.0	12.4	0.492
Allergy history, %	10.0	16.0	0.753
Latency (d), median (25th, 75th)	20 (11,30)	30 (15,70)	0.019
Short latency (<5 days), %	15.0	5.1	0.092
Long latency (>90 days), %	10.0	18.8	0.554
Course of peak ALT decreasing ≥50% after herbal intake discontinuation, median (25 th , 75 th)	8 (5,28)	7 (5,10)	0.446
Positive re-challenge, %	5.0	7.3	1.000
Fever, %	10.0	6.6	0.638
Skin rashes, %	5.0	2.8	0.448
Ascites, %	55.0	9.0	<.001
Encephalopathy, %	40.0	0.9	<.001
Hyponatremia, %	35.0	4.1	<.001
Biochemistries, mean±SD			
Peak ALT (U/L)	752±549	943±676	0.213
Peak ALP (U/L)	250±192	183±110	0.139
Peak TB (mg/dL)	26.7±7.1	9.5±8.6	<.001
Lowest ALB (g/L)	29±4	37±5	<.001
Peak Scr (μmol/L)	104±67	76±32	0.077
Peak TG (mmol/L)	0.95±0.89	1.59±1.33	0.005
Peak TC (mmol/L)	1.35±1.87	3.48±1.76	<.001
Peak INR	2.40±1.31	0.70±0.47	<.001
Blood routine at onset, mean±SD			
White blood cell count (×10 ⁹ /L)	8.20±3.79	5.12±2.14	0.002
Eosinophil count (×10 ⁹ /L)	0.15±0.49	0.25±1.24	0.726
Platelet count (×10 ⁹ /L)	156±79	211±84	0.004
Clinical pattern, %			0.144
Hepatocellular	75.0	86.5	
Cholestatic	15.0	6.0	
Mixed	10.0	7.5	
MELD score, mean±SD	29.6±6.1	12.0±6.3	<.001
Hy's law, %	80.0	66.2	0.201
Cirrhosis, %	10.0	7.5	0.658
Plasma exchange, %	50.0	2.8	<.001
Steroid use, %	10.0	6.6	0.638

*The patients had a drinking history (alcohol intake of >2 drinks per day for women and >3 drinks per day for men) but did not drink a month before the liver injury

ALT: alanine transaminase; ALP: alkaline phosphatase; TB: total bilirubin; ALB: albumin; Scr: serum creatinine; TG: triglyceride; TC: total cholesterol; INR: international normalized ratio; MELD: model for end-stage liver disease

Death and liver transplantation

The clinical characteristics of the 20 patients with a fatal outcome (death or liver transplantation) as compared to the 468 cases in the healed and chronic groups

are summarized in Table 3. The herbs or herbal products associated with death or liver transplantation and their indications are listed in Table 4. Only 3 patients who died were induced by a single implicated herb, such as

Table 4. Herbal preparations associated with death, liver transplantation, and chronic HILI

	Indication	Herbal Preparation
Death/liver transplantation (n=20)	n=7 Skin diseases	n=10 Herbal decoction with unknown constituents.
	n=2 Bone and joint diseases	n=1 Fructus psoraleae; Herbal decoction (<i>Radix codonopsis</i> , <i>Radix ophiopogonis</i> , <i>Pericarpium citri reticulatae</i> , <i>Radix achyranthis bidentatae</i> , <i>Radix glycyrrhizae</i> , <i>Poria</i> , <i>Radix astragali seu hedysari</i> , <i>Semen arecae</i> , <i>Rhizoma alismatis</i> , <i>Rhizoma coptidis</i> , <i>Rhizoma ligustici chuanxiong</i> , <i>Radix paeoniae alba</i> , <i>Caulis polygoni multiflora</i> , <i>Fructus jujubae</i>); <i>Gynura segetum</i> ; <i>Radix polygoni multiflora</i> ; Dan-lu-tong-du tablet (<i>Radix salviae miltiorrhizae</i> , <i>Colla corni cervi</i> , <i>Radix astragali seu hedysari</i> , <i>Rhizoma corydalis</i> , <i>Cortex eucommiae</i>); Gu-kang capsule (<i>Radix musae</i> , <i>Oxalis corniculata</i> , <i>Fructus psoraleae</i> , <i>Radix dipsaci</i> , <i>Radix notoginseng</i>); Long-dan-xie-gan pill (<i>Radix gentianae</i> , <i>Radix bupleuri</i> , <i>Radix scutellariae</i> , <i>Fructus gardeniae</i> , <i>Rhizoma alismatis</i> , <i>Caulis akebiae</i> , <i>Semen plantaginis</i> , <i>Radix angelicae sinensis</i> , <i>Radix rehmanniae recens</i> , <i>Radix glycyrrhizae</i>); Shi-du-qing capsule (<i>Radix rehmanniae recens</i> , <i>Radix angelicae sinensis</i> , <i>Radix salviae miltiorrhizae</i> , <i>Periostracum cicadae</i> , <i>Radix sophorae flavescentis</i> , <i>Cortex dictamni</i> , <i>Radix glycyrrhizae</i> , <i>Radix scutellariae</i> , <i>Rhizoma smilacis glabrae</i>); Shu-gan granule (<i>Radix angelicae sinensis</i> , <i>Radix paeoniae alba</i> , <i>Radix bupleuri</i> , <i>Rhizoma cyperi</i> , <i>Rhizoma atractylodis macrocephalae</i> , <i>Poria</i> , <i>Cortex moutan radicis</i> , <i>Herba menthae</i> , <i>Radix glycyrrhizae</i>) + Bai-ban granule with unknown constituents.
	Health care	
	Endocrine system diseases	
	Urinary diseases	
	n=1 Gastrointestinal diseases	
	Neurological diseases	
	Gynecological disease	
	Cardiovascular diseases	
	Respiratory diseases	
Chronic (n=69)	n=15 Skin diseases	
	n=10 Cardiovascular diseases	n=3 <i>Radix polygoni multiflori</i> .
	n=8 Endocrine system diseases	n=2 Dan-lu-tong-du tablet (<i>Radix salviae miltiorrhizae</i> , <i>Colla corni cervi</i> , <i>Radix astragali seu hedysari</i> , <i>Rhizoma corydalis</i> , <i>Cortex eucommiae</i>); Yan-shou pill (<i>Radix polygoni multiflori</i>); Chinese patent medicine with unknown constituents.
	n=6 Bone and joint diseases	n=1 <i>Tripterygium wilfordii</i> ; <i>Semen cassiae</i> ; Herbal decoction (<i>Radix polygoni multiflori</i> , <i>Fructus lycii</i> , <i>Stigma croci</i>); Herbal decoction (<i>Radix polygoni multiflori</i> , <i>Radix notoginseng</i> , <i>Rhizoma gastrodiae</i> , <i>Radix astragali seu hedysari</i>); Herbal decoction (<i>Radix polygoni multiflori</i> , <i>Poria</i> , <i>Pteridium aquilinum</i> , Black soya bean); Herbal Preparation Herbal decoction (<i>Radix astragali seu hedysari</i> , <i>Rhizoma atractylodis macrocephalae</i> , <i>Radix saposchnikoviae</i> , <i>Ramulus cinnamomi</i> , <i>Radix paeoniae alba</i> , <i>Poria cocos</i> , <i>Rhizoma pinelliae</i> , <i>Radix angelicae sinensis</i> , <i>Radix puerariae</i> , <i>Semen armeniacae amarum</i> , <i>Cortex magnoliae officinalis</i> , <i>Radix codonopsis</i> , <i>Massa medicata fermentata</i> , <i>Radix salviae miltiorrhizae</i> , <i>Radix glycyrrhizae</i> , <i>Rhizoma zingiberis recens</i> , <i>Fructus jujubae</i>); Herbal decoction (<i>Radix polygoni multiflori</i> , <i>Radix ginseng</i> , <i>Radix astragali seu hedysari</i> , <i>Herba hedyotis</i> , <i>Herba scutellariae barbatae</i> , <i>Herba lobeliae chinensis</i> , <i>Herba lysimachiae</i> , <i>Radix bupleuri</i> , <i>Herba artemisiae scopariae</i> , <i>Fructus meliae toosendan</i> , <i>Radix aconiti lateralis preparata</i> , <i>Herba epimedii</i>); Herbal decoction containing <i>Rhizoma alismatis</i> , <i>Radix trichosanthis</i> , and other unknown herbs;
	n=6 Health care	
	Gastrointestinal diseases	
	n=4 Urinary diseases	
	n=3 Gynecological disease	
	n=2 Neurological diseases	
	Breast diseases	
	Hair loss	
	Grey hair	
	n=1 Respiratory diseases	
	Indication	
	Bone and joint disease combined with hair loss	
	Cardiovascular disease combined with urinary disease	

Table 4. Herbal preparations associated with death, liver transplantation, and chronic HILI (Continued)

Indication	Herbal Preparation
	<p>Herbal decoction containing <i>Radix polygoni multiflori</i>, <i>Radix salviae miltiorrhizae</i>, <i>Semen cassia</i>, <i>Fructus crataegi</i>, and other unknown herbs.</p> <p>Ci-gu-yin-xie capsule with unknown constituents;</p> <p>Qu-xuan-ling capsule with unknown constituents;</p> <p>Yang-xue-qing-nao granule (<i>Radix angelica sinensis</i>, <i>Rhizoma ligustici chuanxiong</i>, <i>Radix paeoniae alba</i>, <i>Radix rehmanniae preparata</i>, <i>Ramulus uncariae cum uncis</i>, <i>Caulis spatholobi</i>, <i>Spica prunellae</i>, <i>Semen cassiae</i>, <i>Concha margaritifera</i>, <i>Rhizoma corydalis</i>, <i>Herba asari</i>);</p> <p>Ke-yin pill (<i>Rhizoma smilacis glabrae</i>, <i>Cortex dictamni</i>, <i>Rhizoma menispermi</i>, <i>Rhizoma bistortae</i>);</p> <p>San-qi-yin-xing tea (<i>Radix notoginseng</i>, <i>Folium ginkgo</i>);</p> <p>Wan-mei-sha-ji tea (<i>Fructus hippophae</i>, <i>Fructus momordicae</i>, <i>Citric acid</i>, <i>Fructooligosaccharides</i>, other unknown ingredients);</p> <p>Shen-qi-jian-wei granule (<i>Radix codonopsis</i>, <i>Radix angelicae sinensis</i>, <i>Fructus crataegi</i>, <i>Radix astragali seu hedysari</i>, <i>Poria</i>, <i>Radix glycyrrhizae</i>, <i>Rhizoma atractylodis macrocephalae</i>, <i>Ramulus cinnamomi</i>, <i>Pericarpium citri reticulatae</i>, <i>Caulis perillae</i>, <i>Radix paeoniae alba</i>, <i>Os sepiellae seu sepiae</i>, <i>Radix inulae</i>, <i>Herba taraxaci</i>);</p> <p>Xin-yuan capsule (<i>Radix polygoni multiflori</i>, <i>Radix salviae Miltiorrhizae</i>, <i>Radix rehmanniae recens</i>, other unknown ingredients);</p> <p>Niu-huang-jiang-ya pill (<i>Artificial bezoar</i>, <i>Cornu saigae tataricae</i>, <i>Baicalin</i>, <i>Pearl powder</i>, <i>Semen cassia</i>, <i>Rhizoma ligustici chuanxiong</i>, <i>Borneolum syntheticum</i>, <i>Radix paeoniae alba</i>, <i>Radix curcumae</i>, <i>Radix et rhizoma nardostachyos</i>, <i>Cornu bubali powder</i>);</p> <p>Niu-huang-qing-xin pill (<i>Calculus bovis</i>, Indication Herbal Preparation <i>Radix angelicae sinensis</i>, <i>Rhizoma ligustici chuanxiong</i>, <i>Radix glycyrrhizae</i>, <i>Rhizoma dioscoreae</i>, <i>Radix scutellariae</i>, <i>Semen armeniacae amarum</i>, <i>Semen sojae germinatum</i>, <i>Fructus jujubae</i>, <i>Rhizoma atractylodis macrocephalae</i>, <i>Poria</i>, <i>Radix platycodonis</i>, <i>Radix saposchnikoviae</i>, <i>Radix bupleuri</i>, <i>Colla corii asini</i>, <i>Rhizoma zingiberis</i>, <i>Radix paeoniae alba</i>, <i>Radix ginseng</i>, <i>Massa medicata fermentata</i>, <i>Cortex cinnamomi</i>, <i>Radix ophiopogonis</i>, <i>Radix ampelopsis</i>, <i>Pollen typhae</i>, <i>Moschus</i>, <i>Borneolum syntheticum</i>, <i>Cornu bubali powder</i>, <i>Cornu saigae tataricae</i>, <i>Cinnabaris</i>, <i>Realgar</i>);</p> <p>Bai-xiao pill (<i>Radix et rhizoma rhei</i>, <i>Faeces togopteri</i>, <i>Rhizoma cyperi</i>, <i>Semen pharbitidis</i>, <i>Rhizoma sparganii</i>, <i>Semen arecae</i>, <i>Rhizoma curcumae</i>, <i>Fructus gleditsiae abnormalis</i>, <i>Fructus crataegi</i>, <i>Massa medicata fermentata</i>, <i>Radix glycyrrhizae</i>, <i>Fructus hordei germinatus</i>, <i>Fructus aurantii immaturus</i>, <i>Cortex magnoliae officinalis</i>);</p> <p>Pi-fu-bing-xue-du tablet (<i>Radix rubiae</i>, <i>Semen persicae</i>, <i>Herba schizonepetae</i>, <i>Periostracum serpentis</i>, <i>Radix paeoniae rubra</i>, <i>Radix angelicae sinensis</i>, <i>Rhizoma imperatae</i>, <i>Fructus kochiae</i>, <i>Fructus xanthii</i>, <i>Radix rehmanniae recens</i>, <i>Fructus forsythiae</i>, <i>Flos lonicerae</i>, <i>Herba violae</i>, <i>Rhizoma smilacis glabrae</i>, <i>Cortex phellodendri</i>, <i>Spina gleditsiae</i>, <i>Radix platycodonis</i>, <i>Herba leonuri</i>, <i>Semen armeniacae amarum</i>, <i>Radix saposchnikoviae</i>, <i>Poria</i>, <i>Radix paeoniae alba</i>, <i>Periostracum cicadae</i>, <i>Fructus arctii</i>, <i>Cortex moutan radices</i>, <i>Cortex dictamni</i>, <i>Radix rehmanniae preparata</i>, <i>Radix et rhizoma rhei</i>, <i>Caulis lonicerae</i>, <i>Radix arnebiae</i>, <i>Rhizoma bolbostemmatis</i>, <i>Rhizoma ligustici chuanxiong</i>, <i>Radix glycyrrhizae</i>, <i>Radix angelicae dahuricae</i>, <i>Radix semiaquilegiae</i>, <i>Cercis chinensis</i>, <i>Caulis spatholobi</i>, <i>Herba spirodelae</i>, <i>Flos carthami</i>);</p> <p>Luo-zhen capsule (<i>Folium apocyni veneti</i>, <i>Radix astragali seu hedysari</i>, <i>Radix salviae miltiorrhizae</i>, <i>Rhizoma ligustici chuanxiong</i>, <i>Radix paeoniae alba</i>, <i>Radix curcumae</i>, <i>Semen cassiae</i>, <i>Radix et rhizoma nardostachyos</i>, <i>Herba menthae</i>, <i>Margarita</i>, <i>Cornu saigae tataricae</i>, <i>Radix scutellariae</i>, <i>Calculus bovis</i>, <i>Borneolum syntheticum</i>);</p> <p>Ku-gua-huang-jing capsule (<i>Radix ginseng</i>, <i>Fructus lycii</i>, <i>Semen euryales</i>, <i>Rhizoma polygonati</i>, <i>Flos chrysanthemi</i>, <i>Fructus mori</i>, <i>Rhizoma</i></p>

Table 4. Herbal preparations associated with death, liver transplantation, and chronic HILI (Continued)

	<p><i>polygonati odorati</i>, <i>Radix puerariae</i>, <i>Radix astragali seu hedydari</i>, other unknown ingredients);</p> <p>Jin-gang-teng capsule (<i>Smilax scobinicaulis</i>);</p> <p>E-jiao-bai-zhi oral liquid (<i>Exocarpium benincasae</i>, <i>Colla corii asini</i>, <i>Radix angelicae dahuricae</i>, <i>Endothelium corneum gigeriae galli</i>, <i>Fructus gardeniae</i>, <i>Radix puerariae</i>, <i>Bulbus lillii</i>, <i>Fructus crataegi</i>, <i>Semen persicae</i>, <i>Rhizoma polygonati</i>, <i>Arillus longan</i>);</p> <p>Jing-fu-kang granule (<i>Rhizoma et radix notopterygii</i>, <i>Rhizoma ligustici chuanxiong</i>, <i>Radix puerariae</i>, <i>Radix gentianae macrophyllae</i>, <i>Radix clematidis</i>, <i>Rhizoma atractylodis</i>, <i>Radix salviae miltiorrhizae</i>, <i>Radix paeoniae alba</i>, <i>Lumbricus</i>, <i>Flos carthami</i>, <i>Olibanum</i>, <i>Radix astragali seu hedydari</i>, <i>Radix codonopsis</i>, <i>Radix rehmanniae recens</i>, <i>Concha haliotidis</i>, <i>Ophicalcicum</i>, <i>Cortex phellodendri</i>, <i>Semen vaccariae</i>, <i>Semen persicae</i>, <i>Myrrha</i>, <i>Eupolyphaga seu steleophaga</i>) + Yang-xue-sheng-fa capsule (<i>Radix rehmanniae preparata</i>, <i>Radix angelica sinensis</i>, <i>Rhizoma et radix notopterygii</i>, <i>Fructus chaenomelis</i>, <i>Rhizoma ligustici chuanxiong</i>, <i>Radix paeoniae alba</i>, <i>Semen cuscudae</i>, <i>Rhizoma gastrodiae</i>, <i>Radix polygoni multiflori preparata</i>).</p> <p>Lei-gong-teng tablet (<i>Tripterygium wilfordii</i>) + Herbal decoction with unknown constituents;</p> <p>Yang-xue-sheng-fa capsule + Herbal decoction (<i>Radix rehmanniae preparata</i>, <i>Rhizoma dioscoreae</i>, <i>Fructus corni</i>, <i>Fructus lycii</i>, <i>Radix angelicae sinensis</i>, <i>Radix paeoniae alba</i>, <i>Fructus ligustri lucidi</i>, <i>Fructus mori</i>, <i>Semen sesami nigri</i>, <i>Fructus jujubae</i>, <i>Radix polygoni multiflora</i>, <i>Radix glycyrrhizae</i>, <i>Pericarpium citri reticulatae</i>, <i>Fructus hordei germinates</i>, <i>Fructus crataegi massa</i>, <i>Medicata fermentata</i>, <i>Radix dipsaci</i>, <i>Cortex eucommiae</i>);</p> <p>Ru-kang pill (<i>Concha ostreae</i>, <i>Olibanum</i>, <i>Fructus trichosanthis</i>, <i>Sargassum</i>, <i>Radix astragali seu hedydari</i>, <i>Myrrha</i>, <i>Radix asparagi</i>, <i>Spica prunellae</i>, <i>Rhizoma sparganii</i>, <i>Radix scrophulariae</i>, <i>Rhizoma atractylodis macrocephalae</i>, <i>Bulbus fritillariae thunbergii</i>, <i>Rhizoma curcumae</i>, <i>Radix salviae miltiorrhizae</i>, <i>Endothelium corneum gigeriae galli</i>) + Xiao-yao pill (<i>Radix bupleuri</i>, <i>Radix angelicae sinensis</i>, <i>Radix paeoniae alba</i>, <i>Rhizoma atractylodis macrocephalae</i>, <i>Poria</i>, <i>Radix glycyrrhizae</i>, <i>Herba menthae</i>, <i>Rhizoma zingiberis recens</i>) + Herbal decoction with unknown constituents;</p> <p>Shen-song-yang-xin capsule (<i>Radix ginseng</i>, <i>Radix ophiopogonis</i>, <i>Fructus corni</i>, <i>Radix salviae miltiorrhizae</i>, <i>Semen ziziphi spinosae</i>, <i>Herba taxilli</i>, <i>Radix paeoniae rubra</i>, <i>Eupolyphaga seu steleophaga</i>, <i>Radix et rhizoma nardostachyos</i>, <i>Rhizoma coptidis</i>, <i>Fructus schisandrae chinensis</i>, <i>Os draconis</i>) + Shen-fu-kang capsule (<i>Rhizoma smilacis glabrae</i>, <i>Flos sophorae</i>, <i>Rhizoma imperatae</i>, <i>Herba leonuri</i>, <i>Herba pogostemonis</i>) + Herbal decoction with unknown constituents.</p> <p>Bai-xuan-kang for external usage (<i>Radix sophorae flavescens</i>, <i>Cortex phellodendri</i>, <i>Cortex dictamni</i>, <i>Cortex pseudolaricis</i>, <i>Fructus kochiae</i>, <i>Saussurea involucrata</i>).</p>
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Fructus psoraleae, *Gynura segetum*, and *Radix polygoni multiflora*. Among the 19 lethal cases, 10 (52.6%) died of septic shock, 6 (31.6%) of cerebral edema due to encephalopathy, 2 (10.5%) of hepatorenal syndrome, and 1 (5.3%) of hemorrhagic shock due to upper gastrointestinal bleeding. To predict the fatal prognosis, MELD yielded a C-statistic of 0.981 (95%CI 0.968-0.995), superior to Hy's law (C-statistic 0.569, 95%CI 0.449-0.689) (Figure 2).

Chronicity

In the 468 surviving patients, the comparison of clinical features between the healed (n=399) and chronic (n=69) groups is shown in Table 5. The herbs or herbal products associated with chronic HILI and their indications are listed in Table 4. Only 7 chronic patients were induced by a single implicated herb, including *Radix polygoni multiflori* (n=4), *Tripterygium wilfordii* (n=1), *Semen cassiae* (n=1), and *Smilax scobinicaulis* (n=1). Based on the multivari-

Table 5. Comparison of characteristics between the healed and chronic groups

Characteristic	Healed (n=399)	Chronic (n=69)	p
Age (y), mean±SD	44±14	47±11	0.033
Proportion of patients aged 65 years or older, %	5.8	7.2	0.586
Females, %	71.2	73.9	0.642
Alcohol use*, %	12.5	11.6	0.827
Allergy history, %	16.5	13.0	0.465
Latency (d), median (25th, 75th)	30 (15, 60)	60 (16, 730)	0.001
Short latency (<5 days), %	5.0	5.8	0.768
Long latency (>90 days), %	14.5	43.5	<.001
Course of peak ALT decreasing ≥50% after herbal intake discontinuation, median (25 th , 75 th)	7 (5, 9)	10 (6, 18)	<.001
Positive re-challenge, %	6.8	10.1	0.318
Fever, %	6.5	7.2	0.794
Skin rashes, %	3.0	1.4	0.702
Ascites, %	7.0	20.3	<.001
Encephalopathy, %	0.5	2.9	0.105
Hyponatremia, %	3.5	7.2	0.178
Biochemistries, mean±SD			
Peak ALT (U/L)	987±679	685±604	0.001
Peak ALP (U/L)	184±113	176±92	0.570
Peak TB (mg/dL)	9.7±8.7	8.3±8.4	0.245
Lowest ALB (g/L)	37±4	35±7	0.010
Peak Scr (μmol/L)	75±21	82±68	0.419
Peak TG (mmol/L)	1.69±1.35	0.99±1.04	<.001
Peak TC (mmol/L)	3.48±1.85	3.45±1.18	0.890
Peak INR	0.68±0.48	0.83±0.38	0.006
Blood routine at onset, mean±SD			
White blood cell count (×10 ⁹ /L)	5.18±2.14	4.78±2.11	0.151
Eosinophil count (×10 ⁹ /L)	0.25±1.25	0.23±1.20	0.908
Platelet count (×10 ⁹ /L)	221±81	154±78	<.001
Clinical pattern, %			<.001
Hepatocellular	90.2	65.2	
Cholestatic	3.5	20.3	
Mixed	6.3	14.5	
MELD score, mean±SD	12.0±6.3	12.1±6.8	0.894
Hy's law, %	68.7	52.2	0.007
Cirrhosis, %	1.8	40.6	<.001
Plasma exchange, %	2.5	4.3	0.419
Steroid use, %	5.3	14.5	0.015

*The patients had a drinking history (alcohol intake of >2 drinks per day for women and >3 drinks per day for men) but did not drink a month before the liver injury

ALT: alanine transaminase; ALP: alkaline phosphatase; TB: total bilirubin; ALB: albumin; Scr: serum creatinine; TG: triglyceride; TC: total cholesterol; INR: international normalized ratio; MELD: model for end-stage liver disease

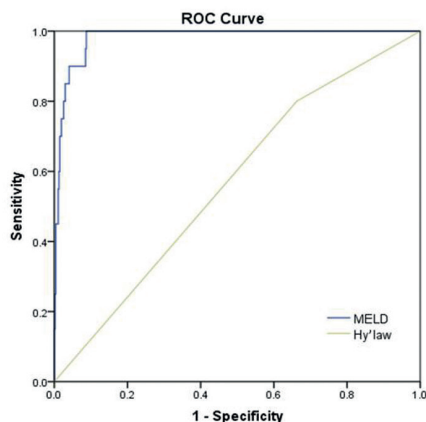


Figure 2. Receiver operating characteristic (ROC) curves to predict the fatal prognosis of HILI: MELD (C-statistic 0.981; 95% CI 0.968-0.995) and Hy's law (C-statistic 0.569; 95% CI 0.449-0.689)

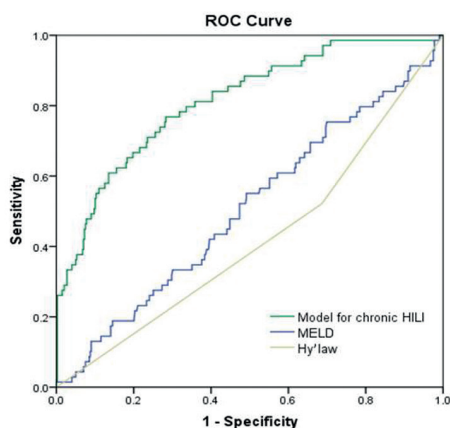


Figure 3. Receiver operating characteristic (ROC) curves to predict the chronic prognosis of HILI: the model for chronic HILI (C-statistic 0.812; 95%CI 0.755-0.868), MELD (C-statistics 0.506; 95%CI 0.431-0.581), and Hy's law (C-statistics 0.418; 95%CI 0.343-0.492)

Table 6. Multivariate logistic regression model predicting chronic HILI

Variables	Adjusted odds ratio (95% confidence interval)	p
Ln (latency, d)	1.268 (1.034-1.554)	0.022
Ln (CA50, d)	2.303 (1.588-3.340)	<0.001
Ln (peak TG value, mmol/L)	0.580 (0.343-0.978)	0.041
Ln (platelet count at liver injury onset, ×10 ⁹ /L)	0.183 (0.091-0.368)	<0.001

CA50: course of peak ALT decreasing ≥50% after herbal intake discontinuation; TG: triglyceride

able logistic regression analysis including age, gender, latency, ascites, peak ALT, lowest albumin (ALB), peak triglyceride (TG), and peak international normalized ratio (INR) values, the course of peak ALT decreasing ≥50% after discontinuation of herbs application (CA50), and platelet count at liver injury onset as covariates, the latency, CA50, peak TG value, and platelet count at liver injury onset predicted chronic HILI with adjusted OR of 1.268 (95%CI 1.034-1.554), 2.303 (95%CI 1.588-3.340), 0.580 (95%CI 0.343-0.978), and 0.183 (95%CI 0.091-0.368), respectively (Table 6).

Based on the latency, CA50, the peak TG value, and platelet count at the liver injury onset, a risk score for chronicity was calculated using the following equation: $4.502 + 0.237 \text{ Ln (latency)} + 0.834 \text{ Ln (CA50)} - 0.545 \text{ Ln (peak TG value)} - 1.699 \text{ Ln (platelet count at liver injury onset)}$. Using a cutoff point of 0.125, this model had a sensitivity of 0.77 and a specificity of 0.72 to predict chronic HILI with a C-statistic of 0.812 (95%CI 0.755-0.868). A similar calculation for Hy's law (C-statistic 0.418; 95%CI 0.343-0.492) and MELD (C-statistic 0.506; 95%CI 0.431-0.581) resulted in lower values (Figure 3).

DISCUSSION

Herbal medicines have been widely and safely used for various diseases and health care for thousands of years (9). Actually, HILI occurred at a low frequency. In a prospective study from a German Traditional Chinese Medicine (TCM) hospital to analyze the frequency of liver injury induced by TCM, only 0.12% patients developed liver injury with ALT ≥ 5 × ULN (10). In this study, only 488 (0.79%) of 61,516 patients hospitalized due to liver injury caused by herbs or herbal products. Among these 488 patients, 18.2% of cases presented poor outcomes mainly for treatment of skin diseases, cardiovascular diseases, and endocrine system diseases.

The diagnosis of HILI is more complicated due to a lack of characteristic biomarkers, compared with liver injury induced by virus, alcohol, and other causes (11). In this study a strict diagnostic criterion of HILI was carried out. First, a biochemistry criterion of HILI was defined to exclude unspecific ALT increases (12). Complete alternative causes of liver injury and pre-existing liver diseases were validly ruled out (13). Detailed medical histories were examined to exclude co-medication with synthetic drugs (3). Moreover, RUCAM was used in this study to assess the causality of herbs and liver injury to further eliminate the substantial background noise of HILI patients (6,10).

Most prognostic scoring systems used in patients with liver injury consider fatal outcome of drug-induced liver injury (DILI); the outcome of HILI has received much less attention (14). Among the prognostic scoring systems, Hy's law and MELD were shown to predict the short-term outcome like death or liver transplantation in DILI patients (15,16). MELD was initially used to prioritize the liver transplant allocation and predict a short-term outcome for patients with end-stage liver disease (8). Subsequently, MELD was found to be a reliable predictor of fatal prognosis of DILI (17). In this study, MELD with a high C-statistic of 0.981 has been proven again to be a good prognostic model for a fatal prognosis of HILI, but not for development of chronicity with a low C-statistic of 0.506. Hy's law, a method to predict a drug's likelihood to induce severe liver injury, stated that in DILI patients, hepatocellular injury and jaundice are associated with a 10% mortality rate (18). Hy's law was a poor predictor for fatal prognosis and was not at all correlated with chronic HILI in this study. Hy's law was developed for predicting serious liver injury induced by synthetic drugs, not herbs in clinical practice; it also focused on short-term mortality rather than chronic liver injury (19).

Herbs, like synthetic drugs, can also cause fatal or chronic liver injury in a small percentage of cases (3,5). Some patients with chronic HILI present cirrhosis (20). No model has yet been forwarded to predict a chronic course in HILI, although chronicity likely developed in 10%-14% of HILI cases in cases series (3,21). Patients with chronic HILI, especially cirrhosis, may need a significantly longer therapy both for the liver injury. However, its mechanism is not yet well understood (22). Persistent liver tissue repair reactions likely are not only an essential part of chronic HILI, but also distinguish it from lethal toxic damages. Risk factors for chronic DILI may be related to hepatocyte injury processes, such as the time of drug intake or hepatocellular functional deficits presenting decreased hepatic triglyceride synthesis (22,23). Chronicity carries a poor HILI prognosis, and its development causes lasting health problem. Special attention should be paid to chronic HILI, and a valid prognostic model of chronic HILI development would aid in the early detection of chronicity.

In this study, we have used the multivariable logistic regression analysis and identified that the latency time, course of ALT decreasing, TG value, and platelet count as covariates are significantly correlated with chronic HILI development. Latency, defined as the time from the beginning of application of implicated agents to the onset of liver injury symptoms, was related to clinical severity

and an unfavorable outcome (23). In this study, patients with long latency were more likely to develop into chronic HILI or cirrhosis than those with short latency. Chronicity and cirrhosis were more common in HILI cases with cholestatic pattern than other patterns. The bile duct damage needs more time to recover in comparison with hepatocellular injury (24). Patients with a low TG value or platelet count, as signals of liver dysfunction and portal hypertension, also had been proven to indicate a poor outcome of liver injury both in patients (25) and in rats (26).

In this study, C-statistic was used to evaluate the predictive ability of models. A C-statistic of 0.7 has a reasonable clinical utility, while a model with a C-statistic of ≥ 0.8 has been considered predictive (17). For a fatal outcome, we calculated a C-statistic value of 0.981 for MELD, in agreement with prior publications (16,27). The prognostic model for chronic HILI based on latency, CA50, TG value, and platelet count predicted chronicity with a C-statistic of 0.812, whereas the C-statistic for MELD and Hy's law were 0.506 and 0.418, respectively. This indicated that the prognostic model for chronic HILI had the best predictive ability.

The conclusions are limited by the fact that all cases were hospitalized in a single center, leading to a low representability for the overall population; this study was a retrospective survey, so missing data could not be supplemented. The prognostic model for chronic HILI was developed based on the data from patients with liver injury induced by herbal medicine, but not for some specific herbs; however, the model still needs validation in multi-center and prospective researches to prove its value for other settings.

In conclusion, herbal medicine is associated with a very low risk of liver injury. MELD was confirmed as a good predictive model of the HILI mortality; for predicting the HILI chronicity, a long latency, a slow recovery, and low triglyceride value and platelet count make the best fit.

Ethics Committee Approval: The authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Since the data for this study were analyzed retrospectively and anonymously, no written informed consent was possible or is necessary.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.Z., J.S.; Design - Y.Z., J.S.; Supervision - Y.Z., X.H.X.; Materials - Y.Z., M.N.; Data Collection and/or Processing - M.N., J.B.W., R.L.W., J.Y.L., Y.L.Z., Y.F.Z., T.T.H., S.M.Y., Y.M.G., F.Z.; Analysis and/or Interpretation - Y.Z., Y.Q.M., X.H.X., J.S.; Literature Search - Y.Z.; Writing manuscript - Y.Z., J.S.; Critical Review - X.H.X., J.S.

Conflict of Interest: The authors have no conflict of interest to declare.

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